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No fee is believed due, however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

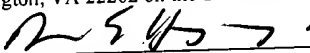

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David E. Huizenga, Ph.D.

April 24, 2002
Date

Appendix A.
Marked-up Specification section

[0051] Two potential impacts of these new findings are significant. First, the role of AR in the modulation of androgen target genes may be expanded. In addition to activation of classic androgen target genes containing androgen response elements (GGA/TACAnnnTGTTCT) (SEQ ID NO:8), AR may also signal through heterodimerization with TR4, resulting in the repression of various TR4 target genes, which contain a consensus response element (AGGTCA) in a DR orientation (AGGTCA(n)_xAGGTCA, x = 0-6) (SEQ ID NOs: 1-7). Data from our gel shift assays showed that the binding preference of TR4 for the natural TR4RE identified in various target genes, was in the order of DRI (CRBII-TR4RE) > DR2 (SV40-TR4RE) > DR4 (TRE-TR4RE) > DR5 (RARE β -TR4RE) > DR3 (VDRE-TR4RE), with the IC₅₀ varying widely from 0.023 ng to 2.0 ng. Lee, et al., *J. Biol. Chem.* 273, 13437-13443 (1998); Lee, et al., *J. Biol. Chem.* 272, 12215-12220 (1997); Lee et al., *J Biol. Chem.* 274, 16198-16205 (1999); Lee et al., *J Biol. Chem.* 270, 30129-30133 (1995). Among these TR4 target genes that could be suppressed by AR, HBV suppression might be especially interesting as it provides the first evidence that AR may play a suppressive role in the HBV expression. Whether this may contribute to the male-preference Hepatitis B or hepatoma will be an interesting topic for future study. Secondly, we have demonstrated that the classic androgen-signaling pathway (AARARE) can be influenced by TR4. This not only represents the first mechanism to distinguish between receptors (AR, GR, and PR) that share the same hormone response elements (found in MMTV or other target genes), but also provides a new potential target through which to block the androgen action. The long-term impact of these two new events may be in providing us another approach in the design of the new generation of drugs with androgenic or antiandrogenic activity with which to treat androgen-related diseases.